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Early Detection of Hepatocellular Carcinoma in Hepatitis-B-Positive Renal Transplant Recipients

S. TANG, MBBS, MRCP (UK),[1] C. M. LO, MBBS, FRCS,[2] T. M. CHAN, MD, FRCP,[1] AND K. N. LAI, MD, FRACP, FACP, FRCP[1]*

[1]*Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong, China*

[2]*Department of Surgery, Queen Mary Hospital, University of Hong Kong, Hong Kong, China*

Hepatocellular carcinoma (HCC) is a leading cause of malignancy after renal transplantation in Asia, where hepatitis B virus infection is endemic. Early detection and resection are the key to successful treatment because the mortality rate for HCC is high. The value of α-fetoprotein monitoring in the early detection of HCC in renal transplant recipients has not been reported before. We describe 2 patients who had successful resection of HCC following early diagnosis by α-fetoprotein monitoring. The epidemiology of post-transplant HCC in various parts of the world and its pathogenesis are discussed.

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KEY WORDS: **hepatitis B infection; hepatocellular carcinoma; renal transplantation; immunosuppression; wedge resection**

INTRODUCTION

Hepatitis B virus (HBV) infection in renal transplant recipients is a progressive disease and a cause of considerable morbidity and mortality [1–3]. Hence, it may be advisable to be extremely cautious when performing transplants in dialysis patients with hepatitis B antigenemia. One of the notable complications of chronic hepatitis B antigenemia is hepatocellular carcinoma (HCC), which, as Penn [4,5] pointed out, is an unusual post–renal transplant complication frequently associated with hepatitis B or C infection. In the Cincinnati Transplant Tumor Registry, with data on 10,813 post-transplant cancers that occurred in 10,151 recipients, HCC accounted for 1% of all the malignancies, or 15% of those involving the hepatobiliary–pancreaticoduodenal area [5].

In Asia, HBV infection is endemic, affecting up to 10% of some populations, as in southern China [6]. HCC is an important cause of mortality in the general population. Surgical cure of HCC relies on early diagnosis before the tumor becomes unresectable due to either bilobar involvement or tumor invasion of the portal venous system. The role of α-fetoprotein (AFP) monitoring in the early detection of HCC in Chinese HBV carriers has been reported previously [7]. However, its value in HBV-positive renal transplant recipients, who may be particularly at risk of developing HCC as a result of concomitant immunosuppression, has not been reported. We report 2 cases in which post-transplant periodic AFP monitoring led to successful cure of HCC.

CASE REPORTS

Case 1

In November 1996, a 63-year-old HBV carrier with unknown cause of end-stage renal failure underwent cadaveric renal transplantation. The pretransplant liver biochemistry was normal. The patient received triple prophylactic immunosuppression with cyclosporin, prednisolone, and azathioprine. There was immediate graft function, with no record of rejection. Three months later, the patient developed neutropenia, which reversed after azathioprine was reduced.

One year later, at a 4-month AFP monitoring, the patient

*Correspondence to: Professor K.N. Lai, Department of Medicine, Queen Mary Hospital, University of Hong Kong, 102 Pokfulam Road, Hong Kong, China. E-mail: knlai@hkucc.hku.hk

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had an elevated AFP level of 188 ng/ml (normal, <20), up from 17 ng/ml 4 months previously. Two-phase dynamic contrast computed tomography (CT) of the liver showed a tumor nodule of 2.1 cm in the lateral aspect of the right lobe. Immunosuppression then included prednisolone, 10 mg qd, and cyclosporin, 100 mg bd. Viral serology was positive for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg). Indocyanine green excretion test showed poor hepatic functional reserve.

The patient underwent wedge resection of the lesion and made an uneventful recovery. Histology showed a well circumscribed but nonencapsulated, moderately well differentiated HCC (2.3 × 2.3 × 2 cm) arranged in a trabecular and sinusoidal pattern, with a clear resection margin. The rest of the liver was cirrhotic. Postoperative AFP level fell progressively to 10 ng/ml, and the patient, currently 14 months after operation, has remained well without recurrence of the tumor on serial ultrasound surveillance. The latest biochemistry showed serum albumin, 44 g/L; alanine aminotransferase (ALT), 24 U/L; aspartate aminotransferase (AST), 35 U/L; and creatinine, 113 μmol/L.

Case 2

In July 1988, a 45-year-old HBV carrier with primary disease of diffuse proliferative glomerulonephritis and receiving home hemodialysis for 4 years received a cadaveric renal transplant. The post-transplant course was uneventful, without rejection episodes. Ten years later, the patient's rising AFP levels (from 10 to 183 ng/ml over a 4-month period) were detected. Viral serology was positive for HBsAg and antibody to HBeAg. Two-phase dynamic CT of the liver showed a 1.5-cm lesion at the lateral segment of the left lobe.

The patient underwent wedge excision of the tumor and made an uneventful recovery. Intraoperative ultrasonography showed no tumor in the rest of the liver. Postoperative AFP fell to 6 ng/ml. Histology showed a moderately well differentiated HCC, with immunostaining showing patchy positivity for AFP. The rest of the liver showed chronic hepatitis with mild activity and fibrosis. There was no recurrence afterward, and the most recent biochemistry, 12 months after the operation, showed serum albumin, 30 g/L; ALT, 25 U/L; AST, 32 U/L; and creatinine, 107 μmol/L.

DISCUSSION

Contrary to the low incidence (1%) reported in Western countries, HCC is a leading cause of post-transplant malignancies in Asia, where HBV is endemic. In a recent analysis from a Taiwanese group of 390 de novo malignancies accumulated over a 13-year observation period, HCC accounted for 34% of all the malignancies [8], similar to a previous Taiwanese report published 6 years ago [9]. Such a high incidence of HCC in renal transplant recipients has also been described by the Japanese in the 1980s [10]. Mortality was >50%. At our center, which comprises the largest group of renal transplant recipients in Hong Kong, HCC accounted for 20% of the cancers encountered.

All these reports and those from the West have focused on the epidemiological aspect, but data are scarce regarding measures to improve the survival of this otherwise rapidly fatal tumor. Although HBV vaccination before dialysis or renal transplants is not always possible in endemic areas, a prime approach to the treatment of post-transplant HCC should begin with early detection followed by eradication therapy. The cases described in the present study illustrate that the value of AFP for early detection of HCC [7] can be extended to renal transplant recipients who are HBV carriers. By the same token, it may also be useful in postoperative surveillance of residual disease and tumor recurrence.

When HCC is diagnosed in its early stage, surgical cure is possible without risking allograft function because reduction of immunosuppression is not always necessary, as in our patients. Wedge resection is a liver-conserving procedure and is a viable alternative to hepatic lobectomy. It can be performed safely for small, solitary lesions despite very poor liver function [11]. Liver volume can be calculated with CT, and hepatic functional reserve can be estimated by measuring the indocyanine green retention rate [12]. These tests may be a guide to decision-making in resectional surgery, although volumetry is not widely performed these days in assessing the risk of liver failure after hepatic resection.

The pathogenesis of HCC in transplant recipients, despite years of research, has remained a mystery. Some have attributed the role of chronic immunosuppression in potentiating the development of HBV-related HCC [13,14]. Both our patients were only on low-dose maintenance immunosuppression (including steroid therapy) and did not have biochemical evidence of chronic hepatitis at the time of developing HCC. This implies that the development of HCC, unlike other post-transplant malignancies, may not be entirely attributable to concurrent immunosuppression. This is further suggested by the fact that only 2 of 47 HBV carriers (mean post-transplant follow-up duration ± SD, 7.8 ± 3.8 years; range, 0.6–15.1) currently under our care have developed HCC. Whereas cirrhosis predisposes to the development of HCC, persistence of HBV alone without cirrhosis is also a direct risk factor for HCC [15]. A close if not causal relationship is observed between chronic HBV infection and the development of HCC on the basis of epidemiologic evidence [16] and laboratory studies [17]. Moreover, HBV has been shown to become integrated into the host genome at the onset of malignant transformation [18].

We conclude that AFP monitoring is important for early detection of HCC in HBV-positive renal transplant patients. Whether this also applies to the general transplant population awaits further studies. Before the exact pathogenesis of HCC is worked out, we recommend regular (3 to 4 months) AFP monitoring for at-risk transplant recipients because early diagnosis and complete resection is the only hope of cure. Once the tumor has developed, its growth is definitely accelerated by immunosuppression [19].

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